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NANOSYS INC. 2625 HANOVER ST. PALO ALTO, CA 94304			NEGIN, RUSSELL SCOTT	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/826,153

Applicant(s)

SCHER ET AL.

Examiner

Russell S. Negin

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2007.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-42, 44-61 is/are pending in the application.
- 4a) Of the above claim(s) 1-25 and 49-59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26-42 and 44-48 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/23/07</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 23 April 2007 are acknowledged and the amendments are entered.

Claims 1-42 and 44-61 are pending in this Office action.

Claims 26-42, 44-48 and 60-61 are examined in this Office action.

Claim Rejections - 35 USC § 112

The rejection of claim 33 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of amendments made by applicant to the set of claims filed on 23 April 2007.

The following rejections are newly applied:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-42, 44-48, and 60-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 recites "a population of nanocrystals comprising an excitation spectrum and an emission spectrum, wherein the emission spectrum and at least a portion of the excitation spectrum are in the nonvisible range." A statutory composition is a

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composition of matter, thus a population of matter should comprise a series of matter. However, here, the composition comprises "an excitation spectrum," etc., which are properties of the matter. It is unclear how a composition of matter "comprises" a property.

Likewise, claim 34 recites "The composition of claim 26, wherein the population of nanocrystals comprises two or more subsets of nanocrystals, the subsets comprising different light wavelengths." In this statement, it is unclear as to how a nanocrystal can be made of a light wavelength.

Likewise, claim 38 recites "The composition of claim 26, wherein the population of nanocrystals comprises two or more subsets of nanocrystals, the subsets comprising different excitation wavelengths." In this statement, it is unclear as to how a nanocrystal can be made of an excitation wavelength.

Likewise, claim 44 recite, "The composition of claim 26, wherein the population of nanocrystals comprises a predetermined excitation spectrum or emission spectrum." In this statement, it is unclear as to how a nanocrystal population can be composed of excitation spectra or emission spectra.

Claim Rejections - 35 USC § 103

The rejections of claims 26-29, 31-32, 34-37, 40, 43, and 46-48 under 35 U.S.C. 103(a) as being unpatentable over Zaheer et al. [Nature Biotechnology, volume 19, December 2001, pages 1148-1154] in view of Bruchez et al. [US Patent 6,274,323,

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issued August 14, 2001] are withdrawn in view of amendments made by applicant to the set of claims filed on 23 April 2007.

The rejections of claims 26, 30 and 38-39 under 35 U.S.C. 103(a) as being unpatentable over Zaheer et al. in view of Bruchez et al. as applied to claims 26-29, 31-32, 34-37, 40, 43, and 46-48 above, and further in view of Bruchez et al. [Science, volume 281, 1998, pages 2013-2016, Information Disclosure Statement, source CA, 19 October 2004] are withdrawn in view of amendments made by applicant to the set of claims filed on 23 April 2007.

The rejections of claims 26, 41-42, and 44-45 under 35 U.S.C. 103(a) as being unpatentable over Zaheer et al. in view of Bruchez et al. as applied to claims 26-29, 31-32, 34-37, 40, 43, and 46-48 above, and further in view of Weiss et al. [WO 00/55631] are withdrawn in view of amendments made by applicant to the set of claims filed on 23 April 2007.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following 35 U.S.C. 103 Rejections are necessitated by applicants' amendments to the set of claims filed on 23 April 2007:

35 U.S.C. 103 Rejection #1:

Claims 26-29, 31-38, 40, 46-48, and 60-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. [Angew. Chem. Int. Ed., 1999, volume 38, pages 3692-3694] in view of Bruchez et al. [US Patent 6,274,323, issued August 14, 2001].

Claim 26 is drawn to a composition comprising a population of nanocrystals comprising an excitation spectrum and an emission spectrum, wherein the emission spectrum and at least a portion of the excitation spectrum are in the nonvisible range; wherein the population of nanocrystals comprises two or more subsets of nanocrystals, the subsets comprising different light emission characteristics, different excitation wavelengths, or different excitation polarization angles; wherein the population of nanocrystals are disposed in or linked to an adherent matrix.

The article of Cao et al. studies the synthesis and characterization of InAs/InP and InAs/CdSe core/shell nanocrystals.

In this article, InAs/InP has an absorbance spectrum in Figure 1.

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In this article, InAs/InP has a fluorescence spectrum in Figure 5.

In this article, InAs/CdSe has an absorbance spectrum in Figure 2.

In this article, InAs/CdSe has a fluorescence spectrum in Figures 2 and 5.

Although the spectra are referred to as absorbance and fluorescence spectra in Cao et al., these terms are synonymous with excitation and emission spectra, respectively. As is stated in Skoog et al. [Fundamentals of Analytical Chemistry, 1992, page 606]:

Relationship between excitation spectra and fluorescence spectra:
Because the energy difference between vibrational states is about the same for both ground and excited states, the absorption spectrum, or excitation spectrum, and the fluorescence spectrum for a compound often appear as mirror images of one another with overlap occurring at the resonance line. This effect is demonstrated by the spectra in Figure 23-2.

Consequently, Figure 23-2 of Skoog et al. illustrates differences between excitation and emission spectra and how they correspond to absorbance and excitation spectra respectively.

The units on the spectra are in eV. Visible light has wavelengths between 400 nm and 700 nm, which corresponds to energies between 3.10 eV and 1.77 eV, respectively. While the absorbance spectra (i.e. excitation spectra) are partially not in the range of visible light described of above, the fluorescence (i.e. emission spectra) are entirely not in the region of visible light as required by the instant claim in Figures 1, 2, and 5 of Cao et al.

While Cao et al. discloses two nanocrystal species, Cao et al. does not disclose mixing the two crystal species into a single population of linking the nanocrystals into an adherent matrix.

The patent of Bruchez et al. uses semiconductor nanocrystals as detectable labels in various chemical and biological species. Bruchez et al. discloses using the nanocrystals as adherents to several types of biopolymer in column 22, line 62 to column 23, line 5, which states:

For example, the semiconductor nanocrystals of the present invention can readily be functionalized to create styrene or acrylate moieties, thus enabling the incorporation of the semiconductor nanocrystals into polystyrene, polyacrylate or other polymers such as polyimide, polyacrylamide, etc ...

Bruchez et al. continues in column 22, lines 23-35 by explaining how matrices and solid supports have the benefit of improved solubility and performance of the linked nanocrystals.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the nanocrystals of Cao et al. by use of the adherent polymers of Bruchez et al. because Bruchez et al. teaches use of the required substrates with the advantages of the increased the solubility and functionality of the nanocrystals. It would have been additionally obvious to modify the two crystals of Cao et al. by producing a mixture of the two crystal types because while each species has the required nonvisible spectra, the mixture of InAs/InP and InAs/CdSe would produce as overlap of spectra, but in the required nonvisible range.

Claim 27 is dependent from claim 26 with the additional limitation of the nanocrystal being a semiconductor nanocrystal.

Claim 28 is dependent from claim 26 with the additional limitation wherein the nanocrystal further comprise a diameter ranging from about 1000 nm to about 0.1 nm.

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Claim 29 is dependent from claim 28 wherein the nanocrystal further comprises a diameter ranging from about 50 nm to about 15 nm.

While Cao et al. does not teach these specific properties of nanocrystals,

Bruchez et al. states in its abstract:

The use of semiconductor nanocrystals as detectable labels in various chemical and biological applications is disclosed. The methods find use for detecting a single analyte, as well as multiple analytes by using more than one semiconductor nanocrystal as a detectable label, each of which emits at a distinct wavelength.

The term "semiconductor nanocrystal" is defined in column 8 of Bruchez et al., lines 59-65:

The terms "semiconductor nanocrystal," "quantum dot," and "Qdot™ nanocrystal" are used interchangeably herein and refer to an inorganic crystallite between about 1 nm and about 10000 nm in diameter or any integer or fraction of an integer therebetween, preferably between about 2 nm and about 50 nm...

Consequently, Bruchez et al. teaches the required properties of nanocrystal type and size.

Claim 31 is dependent from claim 27 with the extra limitation that the coated nanocrystals comprise an inner core, and the coating layer of the semiconductor comprising a band gap greater than that of the core.

Claim 32 is dependent from claim 31 with the extra limitation that the nanocrystals comprise InP.

Claim 33 is dependent from claim 31 with the extra limitation that the coating layer comprises CdSe.

Claim 34 is dependent from claim 26 with the additional limitation of comprising two or more sets of nanocrystals with differing emission wavelengths.

Claim 35 is dependent from claim 26 with the additional limitation of restricting the spectral line widths.

Claim 37 is dependent from claim 26 with the additional limitation of the excitation spectrum comprising ultraviolet, visible, or infrared wavelengths.

Claim 38 is dependent from claim 26 with the additional limitation of comprising two or more sets of nanocrystals with differing excitation wavelengths.

The article of Cao et al. teaches the use of InAs/InP and InAs/CdSe core/shell nanocrystals. Cao et al. also teaches two populations of nanocrystals with differing excitation and emission wavelength characteristics.

Cao et al., however, does not analyze bandgap differences between the cores and the shells of the nanocrystals.

On the subject of spectral widths and bandgaps energies, Bruchez et al. states in column 18, lines 1-5 and lines 19-23:

However, for some applications high information density will not be required and it may be more economically attractive to use more polydisperse particles. Thus, for applications that do not require high information density, the linewidth of the emission may be in the range of 40-60 nm... Suitable materials for the overcoating layer include semiconductor materials having a higher bandgap energy than the semiconductor nanocrystal core.

The use of multiple populations of nanocrystals is described in column 19 lines 23-26 of Bruchez et al.

The above method can be used to prepare separate populations of semiconductor nanocrystals, wherein each population exhibits a different characteristic photoluminescence spectrum.

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It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the plurality of nanocrystals studied by Cao et al. by use of the bandgap analysis of Bruchez et al. because Bruchez et al. has the advantage of being used to produce separate populations of semiconductor nanocrystals with each population having a specified and unique photoluminescence spectrum.

Claim 36 is dependent from claim 26 with the additional limitation that the nanocrystals are manufactured by colloidal synthesis.

Columns 1 and 2 of pages 3694 of Cao et al. describe the colloidal synthesis process of the nanocrystals.

Claim 40 is dependent from claim 26 wherein the emission spectrum comprises nonvisible wavelengths.

In Cao et al., the emission spectra have energies less than 1.77 eV, indicating that they are infrared (i.e. wavelength greater than 700 nm).

Claim 46 is dependent from claim 26 with the additional limitation that the adherent matrix comprises a polymer.

Claim 47 is dependent from claim 26 with the additional limitation that the composition is excitable or detectable through a barrier.

Claim 48 is dependent from claim 47 with the additional limitation that the barrier comprises animals.

Claim 60 is dependent from claim 26 with the additional limitation that the population of nanocrystals linked to an adherent matrix, which adherent matrix comprises an affinity molecule of an antibody.

Claim 61 claims an object tagged with the composition of claim 26.

Cao et al. does not describe polymers as adherent matrices or the use of animals as barriers.

Bruchez et al., however, states that polymers or animals can be used as detectable barriers for the semiconductor nanocrystals.

The patent of Bruchez et al. uses semiconductor nanocrystals as detectable labels in various chemical and biological species. Bruchez et al. discloses using the nanocrystals as adherents to several types of biopolymer in column 22, line 62 to column 23, line 5, which states:

For example, the semiconductor nanocrystals of the present invention can readily be functionalized to create styrene or acrylate moieties, thus enabling the incorporation of the semiconductor nanocrystals into polystyrene, polyacrylate or other polymers such as polyimide, polyacrylamide, etc ...

Consequently, the polymers or biopolymers are the affinity molecules and objects tagged with the nanocrystals.

Bruchez et al. continues on column 23, lines 50-60 by explaining that the semiconductor nanocrystals can be used in animals in which animals themselves are the barriers.

35 U.S.C. 103 Rejection #2:

Claims 30 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. in view of Bruchez et al. as applied to claims 26-29, 31-38, 40, 46-48, and 60-61 above, and further in view of Bruchez et al. [Science, volume 281, 1998, pages 2013-2016, Information Disclosure Statement, source CA, 19 October 2004].

This second Bruchez reference will be referred to as "Bruchez et al. (1998)."

Claim 30 depends from claim 27 with the additional limitation that the production of the nanocrystals employs the usage of substituted silanes.

Claim 39 depends from claim 38 with the additional limitation that wavelengths that are alternately excited with different excitation wavelengths.

Cao et al. in view of Bruchez et al. as applied to claims 26-29, 31-38, 40, 46-48, and 60-61 above fail to teach use of substituted silanes or alternating wavelengths.

The article of Bruchez et al. (1998) investigates semiconductor nanocrystals as fluorescent biological labels and states in the abstract:

Semiconductor nanocrystals were prepared for use as fluorescent probes in biological staining and diagnostics. Compared with conventional fluorophores, the nanocrystals have a narrow, tunable, symmetric emission spectrum and are photochemically stable. The advantages of the broad, continuous excitation spectrum were demonstrated in the dual emission, single excitation labeling experiment on mouse fibroblasts. These nanocrystal probes are thus complementary and in some cases may be superior to existing fluorophores.

Figure 2 shows more than one light emission wavelength distribution with the appropriate spectral widths (about 25 to 30 nm) illustrated in the figure. Figure 1 of Bruchez et al. (1998) illustrate more than one excitation wavelength. There is more than one excitation peak in Figure 1B, corresponding to different excitation wavelengths alternately.

Bruchez et al. (1998) ends the article by stating:

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The development of nanocrystals for biological labeling opens up new possibilities for many multicolor experiments and diagnostics. Further, it established a class of fluorescent probe for which no small organic molecule equivalent exists. The tunability of the optical features allows for their use as direct probes or as sensitizers for traditional probes. These nanocrystals have long fluorescent lifetimes (hundreds of nanoseconds), which can allow for time-gated detection for autofluorescence suppression. Further development, such as direct immunolabeling, in situ hybridization, and incorporation into microspheres will be important for applications such as cytometry and immunocytobiology. In addition nanocrystal probes may prove useful for other contrast mechanisms such as x-ray fluorescence, x-ray absorption, electron microscopy, and scintillation proximity imaging, and the use of for-red or infrared-emitting nanocrystals (InP and InAs) as tunable, robust infrared dyes is another possibility.

Footnote number 20 on page 2015 of Bruchez et al. (1998) shows how the nanocrystals are synthesized using substituted silanes and the formation of polymers (footnotes 20 and 22). Use of silanes is a widely accepted procedure for generating nanocrystals.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the inventions of Cao et al. in view of Bruchez et al. as applied to claims 26-29, 31-38, 40, 46-48, and 60-61 above, and further in view of Bruchez et al. (1998) because Bruchez et al. (1998) has the advantage of improving a common technique in the art (use of silanes to make nanocrystals) to generate the nanocrystals with tunable wavelengths; this improvement results in better performance of biological measurement techniques (i.e. X-ray fluorescence, x-ray absorption, and scintillation proximity imaging).

35 U.S.C. 103 Rejection #3:

Claims 41-42, and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. in view of Bruchez et al. as applied to claims 26-29, 31-38, 40, 46-48, and 60-61 above, and further in view of Weiss et al. [WO 00/55631].

Claim 41 depends from claim 26 with the additional limitation that a subset of the nanocrystals comprises a predetermined intensity of emission at a wavelength.

Claim 42 depends from claim 41 with the additional limitation that the intensity is predetermined by varying concentration of a nanocrystal constituent.

Claim 44 depends from claim 26 with the additional limitation that the population of nanocrystals comprises a predetermined excitation spectra or emission spectra.

Claim 45 depends from claim 44 with the additional limitation of varying the size of the nanocrystal.

Cao et al. in view of Bruchez et al. as applied to claims 26-29, 31-38, 40, 46-48, and 60-61 above fail to teach variance of concentration of a constituent and its effects on spectra.

The patent of Weiss et al. investigates nanocrystal probes for biological applications and states on page 14, lines 14-20:

Furthermore, the frequency and wavelength of the narrow wavelength band of light emitted from the semiconductor nanocrystal may be further selected according to the physical properties, such as size, of the semiconductor nanocrystal. The wavelength band of light emitted by the semiconductor nanocrystal, formed using the above embodiment, may be determined by either (1) the size of the core, or (2) the size of the core and the size of the shell...

On page 15, lines 5-12, Weiss et al. states, "Selection of the emission wavelength by varying the composition, or alloy, of the semiconductor nanocrystal is old in the art. As an illustration, when CdS semiconductor nanocrystal, having an emission wavelength of 400 nm, may be alloyed with a CdSe semiconductor nanocrystal, having an emission wavelength of 530 nm."

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On page 53, lines 12-28, Weiss et al. explains the advantages of using their semiconductor nanocrystals:

Thus, the invention provides an semiconductor nanocrystal probe containing a semiconductor nanocrystal capable, upon excitation by either electromagnetic radiation (of either narrow or broad bandwidth) or particle beam, of emitting electromagnetic radiation in a narrow wavelength band and/or absorbing energy and/or scattering or diffracting said excitation, thus permitting the simultaneous usage of a number of such probes emitting different wavelengths of electromagnetic radiation to thereby permit simultaneous detection of the presence of a number of detectable substances in a given material. The probe material is stable in the presence of light or oxygen, capable of being excited by energy over a wide spectrum, and has a narrow band of emission, resulting in an improved material and process for the simultaneous and/or sequential detection of a number of detectable substances in a material such as a biological material.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to practice the inventions of Cao et al. in view of Bruchez et al. as applied to claims 26-29, 31-38, 40, 46-48, and 60-61 above, and further in view of Weiss et al. [WO 00/55631] because Weiss et al. has the advantage of detecting multiple substances simultaneously using a given wavelength of excitation relevant to biological applications.

Response to Arguments

Applicant's arguments filed 23 April 2007 have been fully considered and they are persuasive in light of the amended set of claims also filed on 23 April 2007.

In light of amendments to claim 33 and arguments on pages 12-13 of the Remarks, the enablement rejection is withdrawn.

In light of amendments to the remaining set of claims and arguments made by applicant pertaining to the prior art rejections based on the amended set of claims, previous prior art rejection were withdrawn, while new prior art rejections are enacted.

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Conclusion

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Ram Shukla, Supervisory Patent Examiner, can be reached at (571) 272-0735.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

 7/19/07

RSN
19 July 2007

/Shubo (Joe) Zhou/

SHUBO (JOE) ZHOU, PH.D.
PRIMARY EXAMINER